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TITLE: A Prospecitve, Randomized Clinical Trial of Celecoxib for the Control of Symptomatic Plexiform Neurofibroma in Neurofibromatosis 1

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13. ABSTRACT (Maximum 200 Words)
The purpose of the project was to develop the infrastructure necessary to run a multi-center clinical trial of a novel medical therapy for patients with NF1. To this end, a consortium of seven institutions was developed, each with expertise in treating patients with NF1 or tumors of the nervous system. Important accomplishments include the establishment of a clinical protocol for running the trial; naming a Steering Committee, Data and Safety Monitoring Board, and Medical Monitor; and partnering with Pfizer, Inc. and PharmaContent, Inc. to run the trial. The protocol was submitted for approval at the Institutional Review Board at the sponsoring institution. This work culminated in the submission of a application for a Clinical Trial Award through the Department of Defense in June, 2005 (month 6 of the grant period).

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Introduction

The subject of award W81XWH-04-1-0119 entitled "A prospective randomized clinical trial of celecoxib for the control of symptomatic plexiform neurofibroma in neurofibromatosis 1" was development of a clinical trial for patients with plexiform neurofibromas and neurofibromatosis 1 (NF1). The purpose of the project was to develop the infrastructure necessary to run a multi-center clinical trial of a novel medical therapy for patients with NF1. To this end, a consortium of seven institutions was developed, each with expertise in treating patients with NF1 or tumors of the nervous system. This work culminated in the submission of a application for a Clinical Trial Award through the Department of Defense in June, 2005 (month 6 of the grant period).

Body

The research accomplishments completed in the course of this award are described below with reference to the approved Statement of Work.

Task1: Develop research protocol, months 1-4

A detailed research protocol was developed by the team at Massachusetts General Hospital. This protocol included a description of the specific aims, analysis of patient availability and enrollment goals, determination of inclusion criteria, determination of exclusion criteria, and study procedures. Issues addressed in study procedures includes informed consent/assent, mechanism of randomization and blinding, dosing schedule for adults and children, content of all study visits, clinical assessments (study endpoints), and off-study criteria. Other issues addressed include the participation of children in a drug study, intent to benefit, risk/benefit analysis, and protection of human subjects.
A mechanism was established for obtaining drug and placebo from Pfizer, Inc. and distributing them to study sites in blinded fashion. A plan for ensuring safety was established an included details for adverse event reporting, unblinding, dose and modification. With a collaboration with statisticians at the Harvard School of Public Health, an appropriate statistical plan was established with power calculations, safety stopping and futility rules, and analysis of all study endpoints. A detailed plan for project coordination and data management was established. This plan included details for communication among the coordinating center, study sites (including IRBs), the DSMB, the Steering Committee, the Medical Monitor, the FDA, and the Department of Defense. A data management plan was established with transfer of all study information via the internet using accepted security procedures. A collaboration with PharmaContent, Inc. was established to provide the computer software necessary to provide this electronic communication securely. The research protocol was submitted to PI's at seven institutions for revision and approval.

Seven clinical sites with Principal Investigators were identified: Massachusetts General Hospital (Dr. Scott Plotkin), Duke University (Dr. Henry Friedman), National Cancer Institute (Dr. Brigitte Widemann), University of Alabama at Birmingham (Dr. Alyssa

Reddy), University of California at San Francisco (Dr. Kelly Nicholas), Washington University at St. Louis (Dr. Allison King), and D.C. Children's National (Dr. Tena Rosser).

A collaboration with Pfizer, Inc. was established with the company agreeing to supply study drug and placebo free of charge for the study and for one-year after completion of the study.

Task 2: Operationalize the research protocol at host institutions, months 4-6

The study protocol was submitted to the Institutional Review Board at Massachusetts General Hospital. Included in this packet were adult consent forms for the coordinating center, model adult consent forms for study sites, assent forms (age 7-11) for the coordinating center, model assent forms for study sites (age 7-11), assent forms (age 12-17) for the coordinating center, model assent forms for study sites (age 12-17), a Coordinating Center Umbrella Protocol, and a sample recruitment letter.

A Data and Safety Monitoring Board (DSMB) consisting of Drs. Carl Leventhal, Myunghee Paik, and Thomas DeLaney was assembled. A Steering Committee consisting of Drs. Scott Plotkin, Mia MacCollin, James Gusella, Merit Cudkowicz, Rebecca Betensky, and Bruce Korf was assembled. Dr. Eric Smith was named as the Medical Monitor.

An Investigational New Drug application was submitted to the Food and Drug Administration and granted during the grant period (IND#70,151).

Task 3: Develop an infrastructure to coordinate the five site institutions, months 4-9

A methodology for collection and digitalization of MRI scans was partly developed during the grant period. Detailed protocols for collection of appropriate MRI sequences was developed by Dr. Hamid Salamipour. Volumetric analysis of plexiform neurofibromas was developed and validated by Dr. Gordon Harris. A method for transferring MRI scans electronically was not finalized prior submission of the Clinical Trial Award to the Department of Defense in June, 2005 (Month 5).

A real-time, web-based method of data entry was developed in conjunction with PharmaContent, Inc. The details of the web-based format with adequate security controls was finalized. Work was initiated on developing case report forms for the study when the Clinical Trial Award was submitted to the Department of Defense in June, 2005 (Month 5).

A site monitoring plan was drafted with details concerning the role of site monitors in assuring the accuracy of informed consent documents, case report forms, adverse event forms, and IRB approval at study sites.

Task 4: Operationalize the research protocol at collaborating institutions, months 7-12

Subtasks under task 4 were not finalized prior submission of the Clinical Trial Award to the Department of Defense in June, 2005, in Month 5.

Key Research Accomplishments

- Collaboration of seven clinical sites with interest and expertise in conducting clinical trial for patients with NF1
- Development of a clinical research model for studying efficacy of investigational drugs for plexiform neurofibromas
- Establishment of partnerships with Pfizer, Inc to supply drug and placebo for the study
- Establishment of partnership with PharmaContent, Inc. to design real-time, web-based method for collecting study data among multiple study sites

Reportable Outcomes

Based on the work performed under this grant, an application for a Clinical Trial Award was submitted to the Department of Defense in June, 2005 (NF043127).

Conclusions

The application for a Clinical Trial Award submitted in June, 2005, was not granted. However, the resources committed under the Clinical Trial Development Award were instrumental in developing a comprehensive plan to stage a multi-center, randomized clinical trial for patients with plexiform neurofibromas and NF1.

References

None

Appendices

None